The specification has been amended to include the required references to sequence identification numbers of the Sequence Listing filed concurrently herewith, to indicate the insertion point for the Sequence Listing, and to correct a typographical error on page 25 (line 18; "without"), No new matter has been introduced by this amendment. An Appendix including a marked-up copy of the amendments is attached, showing the changes. The attachment is captioned **"Version with markings to show changes made."**

I hereby state that the content of the paper and computer readable copies of the Sequence Listing submitted in accordance with 37 C.F.R. §1.821(c) and (e), respectively, are the same.

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(g), herein does not include new matter.

A copy of the notice to comply is enclosed.

Respectfully submitted,

February 5, 2002
Date

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please replace the paragraph bridging pages 5 and 6 with the following rewritten paragraph:

Protein-based serine protease inhibitors have been evaluated to block furin activity. The most specific one is an engineered variant of the endogenous elastase inhibitor, the serpin α_1-antitrypsin (α_1-AT). To engineer this derivative, Anderson *et al.* have mutated the natural reactive site (Ala-Ile-Pro-Met^{358} [SEQ ID NO: 1]) of the serpin for an Arg-Ile-Pro-Arg^{358} (SEQ ID NO: 2) sequence (reference 37). This mutant named PDX now mimics the minimum consensus sequence (R-X-X-R) required for furin recognition and has been shown to be a potent furin inhibitor *in vitro* and in cells (references 37 and 38). Recent studies using purified enzymes have demonstrated that PDX is a potent inhibitor of furin that also inhibits PC6 to some extent (references 39 and 40). PDX has also been shown to block furin activity in an *in vitro* measles virus model resulting in loss of syncitia formation (reference 41). Thus, PDX offers an interesting approach to address the role of furin in pathological conditions.

Please replace the 6th paragraph on page 8 (lines 17-18) with the following rewritten paragraph:

Figure 5B depicts the effect of Dec-RVKR-CH_2Cl (SEQ ID NO: 3) on TACE maturation in LoVo cells.

Please replace the 8th paragraph on page 8 (lines 23-24) with the following rewritten paragraph:

Figure 5D depicts the effect of Dec-RVKR-CH_2Cl (SEQ ID NO: 3) on TNF α release from MonoMac-1 cells.

Please replace the paragraph bridging pages 24 and 25 with the following rewritten paragraph:

To define if proprotein convertases other than furin are involved in TACE maturation, LoVo NEO cells were incubated for 24 hrs in the presence of Dec-RVKR-CH_2Cl (SEQ ID NO: 3), a synthetic peptide that mimics proprotein recognition site. Such inhibitor has been shown to efficiently inhibit the enzymatic activity of most members of the proprotein convertases including furin, PC6B, PC3, PC2, PACE-4 and PC7 (48). LoVo NEO cells were incubated for 24 hrs in the presence of various concentrations of Dec-RVKR-CH_2Cl (SEQ ID NO: 3), and cell lysates were assessed for TACE maturation by Western blotting as described above. As shown in Fig. 5B, the addition of Dec-RVKR-CH_2Cl (SEQ ID NO: 3) to LoVo NEO cells results in a further inhibition of TACE maturation, clearly indicating that other proprotein convertases family members than furin are involved in TACE maturation.

Please replace the paragraph bridging pages 25 and 26 with the following rewritten paragraph:

TACE has been shown to mediate cleavage of TNFα as well as a variety of ectodomain including the TNF p75 receptor (49). To investigate whether the levels of TACE maturation observed in LoVo transfectants impacts TACE-related activities, we first measured cell-surface p75 TNF receptor expression as a marker for TACE cell-surface activity. Briefly, LoVo NEO and LoVo FUR2 cell samples were labeled with anti-TACE or anti-TNF p75 receptor antibodies (Catlag laboratories, Burlingame, CA) and cell fluorescence was analyzed on a FACScan (Becton Dickinson). Results expressed in Fig. 5C, indicated that furine complementation of LoVo cells reduces cell-surface p75 TNF receptor expression (48% reduction) without affecting the levels of cell surface TACE. Next, we measured the ability of Dec-RVKR-CH_2Cl (SEQ ID NO: 3) to block TNFα release from MonoMac-1 cells, a human monocytic cell line known to produce high levels of this cytokine (50). For this, MonoMac-1 cells were preincubated for 22 hrs with varying concentrations of Dec-RVKR-CH_2Cl (SEQ ID NO: 3), then 500 ng/ml LPS and 100 ng/ml PMA were added. After 3 hours incubation with PMA and LPS, the supernatants were tested for TNF-α production using a TNF-α-specific ELISA assay

(R&D Systems, Minneapolis, MN). Results expressed in Fig. 5D indicated that treatment of these cells with a proprotein convertase inhibitor blocked almost completely TNFα released with an ED 50 obtained around 20 μM. These results suggest that inhibition of TACE processing leads to an impairment in TACE activities.